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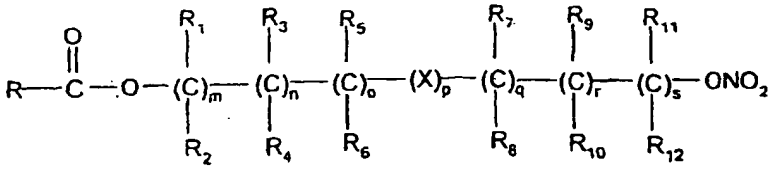
(54) Title: PROCESS FOR PREPARING NITROOXYDERIVATIVES OF NAPROXEN



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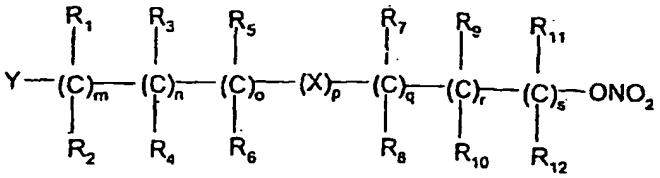

(B)

(57) Abstract: The present invention refers to a process for preparing a compound of general formula (A), wherein R is a radical of naproxen or bromonaproxen and R_1-R_{12} are hydrogen or alkyl groups, m, n, o, q, r and s are each independently an integer from 0 to 6, and p is 0 or 1, and X is O, S, SO, SO_2, NR_{13} or PR_{13}or an aryl, heteroaryl group, said process comprising reacting a compound of formula (B) : R-COOZ wherein R is as defined above and Z is hydrogen or a cation selected from: Li+, Na+, K+, Ca++, Mg++, tetralkylammonium, tetralkylphosphonium, with a compound of formula (C), as reported in the description, wherein R1-R12 and m, n, o, p, q, r, s are as defined above and Y is a suitable leaving group.

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For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.

PROCESS FOR PREPARING NITROOXYDERIVATIVES OF NAPROXEN

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The present invention relates to a process for preparing nitrooxyalkylesters of naproxen (2-(S)-(6-methoxy-2-naphtyl)-propanoic acid) or bromonaproxen (2-(S)-(5-bromo-6-methoxy-2-naphtyl)-propanoic acid) (Tetrahedron 1989, Vol 45, pages 4243-4252).

It is well known in the prior art that the anti-inflammatory activity of (2-(S)-(6-methoxy-2-naphtyl)-propanoic acid) is due to the S enantiomer which is the product in the market (Naproxen).

WO 01/10814 discloses a process for preparing the nitroxybutylester of the 2-(S)-(6-methoxy-2-naphtyl)-propionic acid by reacting the (2-(S)-(6-methoxy-2-naphtyl)-propionyl chloride with 4-nitrooxybutan-1-ol in methylene chloride and in presence of potassium carbonate. The obtained ester has an enantiomeric excess (e.e.) higher than or equal to 97%. This method has the disadvantage that several by-products are formed, being in fact very difficult to obtain nitrooxyalkyl alcohols in pure form and 2-arylpropanoyl halides of high chemical and enantiomerical purity. Moreover, for example 4-nitrooxybutan-1-ol is stable only in solution and it cannot be isolated as a pure substance.

The present invention provides a new process for preparing nitrooxyalkylesters of naproxen or bromonaproxen having an enantiomeric excess as high as that of the starting naproxen or bromonaproxen wherein impurities and by-products are present in an essentially negligible amount. Therefore, starting from enantiomerically pure Naproxen, enantiomerically pure esters are obtained. This is of

particular importance because : i) most of the nitrooxyalkyl esters of Naproxen are low melting point or liquid substances, consequently the e.e. of the obtained crude esters cannot be enhanced by conventional physical methods ii) the absence of functional groups, apart from the ester one, in the molecules under consideration makes the purification problematic.

Another advantage of the present invention is that the starting compounds are stable. The process of the present invention uses as starting material a salt of Naproxen and a nitrooxy alkyl derivative having a leaving group, as substituent, in the alkyl chain.

Naproxen salt is used as ammonium or alkaline metals salt.The sodium salt is chemically and enantiomerically stable and, and is commercially available instead of 2-(S)-(6-methoxy-2-naphtyl)-propanoyl chloride (Naproxen chloride),is not commercially available in large scale, is chemically unstable and easy to racemize.

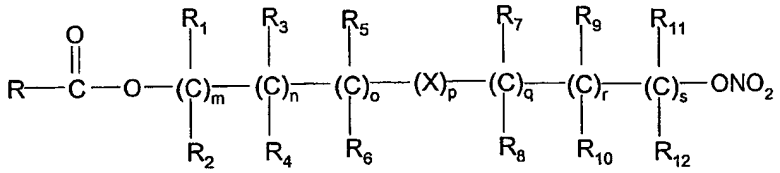
Also the nitrooxy alkyl derivative are more stable in comparison to the corresponding nitrooxyalkyl alcohol. Therefore both reagents involved in the present process, are by far more stable in comparison to those reported in the prior art.

The observed high selectivity of the process was unexpected, because of the presence of two substituents on the nitrooxy alkyl derivative, the nitrooxy and the leaving group, which were expected to compete in the displacement reaction by the Naproxen salt with concomitant loss of process selectivity. Another advantage of the present invention is that the starting compounds are stable. The process of the present invention uses as starting material naproxen salt, instead of the acid chloride of the prior

art process, in particular the sodium salt which is a stable and commercially available product.

Bromonaproxen nitroxooyakylesters are per se biologically active and can be converted into the corresponding naproxen esters by conventional method.

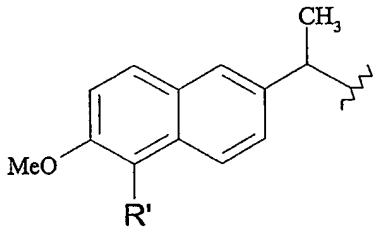
The present invention relates to a process for preparing a compound of general formula (A)



(A)

wherein:

R is



in which R' is a hydrogen atom or Br

R_1-R_{12} are the same or different and independently are hydrogen, straight or branched C_1-C_6 alkyl, optionally substituted with aryl;

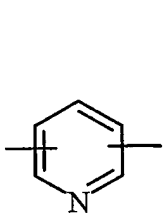
m, n, o, q, r and s are each independently an integer from 0 to 6, and p is 0 or 1, and

X is O, S, SO, SO_2, NR_{13} or PR_{13}, in which R_{13} is hydrogen, C_1-C_6 alkyl, or X is selected from the group consisting of:

- cycloalkylene with 5 to 7 carbon atoms into cycloalkylene ring, the ring being eventually substituted with side chains T, wherein T is straight or branched alkyl with from 1 to 10 carbon atoms, preferably CH_3;

- arylene, optionally substituted with one or more halogen atoms, straight or branched alkyl groups containing from 1 to 4 carbon atoms, or a straight or branched C_1-C_3 perfluoroalkyl;

- a 5 or 6 member saturated, unsaturated, or aromatic heterocyclic ring selected from



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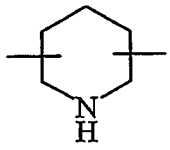

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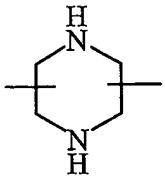

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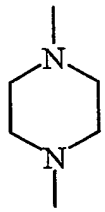

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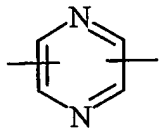

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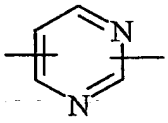

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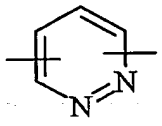

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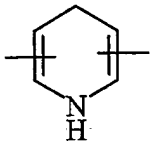

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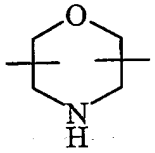

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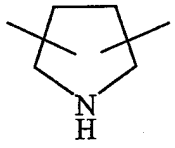

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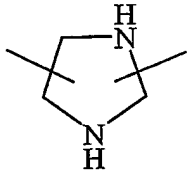

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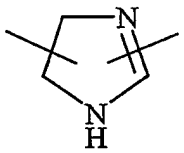

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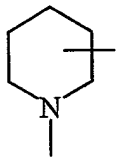


(X13)

wherein the bonds, when they have an undefined position, are intended to be in any possible position in the ring;

said process comprising

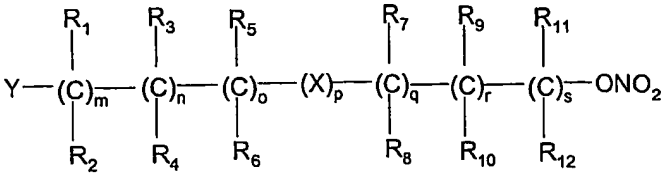
i) reacting a compound of formula (B)

R-COOZ (B)

wherein R is as above defined and Z is hydrogen or a cation selected from:

Li+, Na+, K+, Ca++, Mg++, ammonium, trialkylammonium tetralkylammonium and tetralkylphosphonium;

with a compound of the following formula (C)



(C)

wherein R_1-R_{12} and m,n,o,p,q,r,s are as defined above and Y is selected from

- a halogen atom
- $-BF_4$, $-SbF_6$, FSO_3-, ClO_4-, R_ASO_3-, in which R_A is a straight or branched C_1-C_6 alkyl, optionally substituted with one or more halogen atoms, or a C1-C6 alkylaryl;
- R_BCOO^-, wherein R_B is straight or branched C_1-C_6 alkyl, aryl, optionally substituted with one or more halogen atoms or NO_2 groups, C_4-C_{10} heteroaryl and containing one or more heteroatoms, which are the same or different, selected from nitrogen, oxygen sulfur or phosphorus;
- aryloxy optionally substituted with one or more halogen atoms or NO_2 groups, or heteroaryloxy and

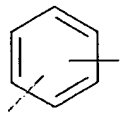
ii) optionally converting a compound of formula (A) wherein R' is Br into a compound of formula (A) wherein R' is hydrogen.

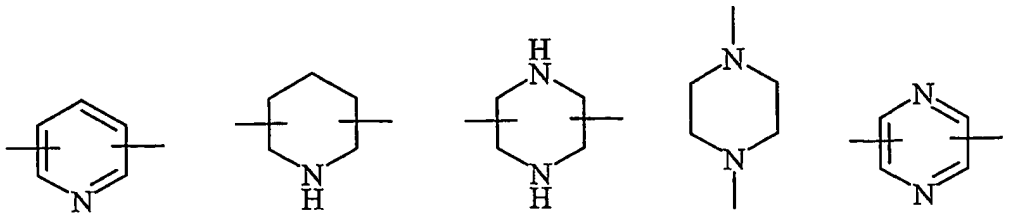
Preferably the present invention relates to a process for preparing a compound of formula A as above defined wherein:

the substituents R_1-R_{12} are the same or different and independently are hydrogen or straight or branched C_1-C_3 alkyl,

m, n, o, p, q, r and s are as defined above,

X is O, S or





(X1) (X2) (X3) (X4) (X5) .

Most preferably the invention relates to process for preparing a compound of formula A according to claim 1 or 2 wherein R_1-R_4 and R_7-R_{10} are hydrogens, m, n, q, r, are 1, o and s are 0, p is 0 or 1, and X is O or S.

In the compounds of formula (C), preferably Y is selected from the group consisting of Br, Cl, I, $-BF_4$, ClO_4^-, $-SbF_6$, FSO_3-, CF_3SO_3-, $C_2F_5SO_3-$, $C_3F_7SO_3-$, $C_4F_9SO_3-$, $p-CH_3C_6H_4SO_3-$.

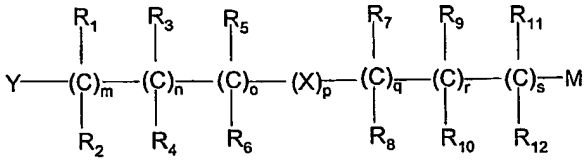
The reaction between a compound of formula (B) and a compound of formula (C) may be carried out in an organic solvent selected from acetone, tetrahydrofurane, dimethylformamide, N-methylpyrrolidone, sulfolane and acetonitrile.

Alternatively the reaction may be carried out in a biphasic system comprising an aprotic dipolar solvent selected from toluene, chlorobenzene, nitrobenzene, tert-butyl-methylether and a water solution wherein the organic solution contains (C) and the water solution contain an alkaline metal salt of (B), in presence of a phase transfer catalyst such as onium salts, for example tetralkylammonium and tetralkylphosphonium salts.

The reaction is carried out at a temperature ranging from 0°C to 100°C and at a (B)/(C) molar ratio of 2-0.5.

The carboxylic acid salt may be prepared separately or can be generated *"in situ"*, for example performing the reaction between (B) and (C) in the presence of a stoichiometric amount of a tertiary amine, or employing an amount in excess of said amine.

The compounds of formula (C),may be prepared by nitrating compounds of formula (D) reported here below, with nitrating agents selected for example, sulfonitric mixture and the like:

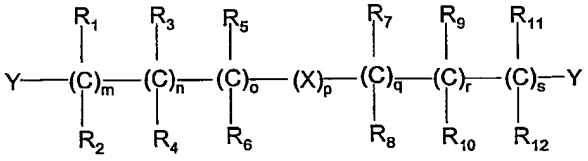


(D)

wherein M is OH, and

Y, X, m, n, o, p, q, r, s and R_1-R_{12}, have the meanings mentioned above.

Alternatively the compounds of formula (C) may be obtained by reacting a compound of formula (E) with nitrating agents selected for example from alkaline metal nitrates, quaternary ammonium nitrates, quaternary phosphonium salts and $AgNO_3$, $Zn(NO)_2.6H_2O$:

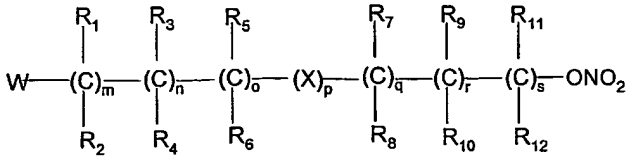


(E)

wherein:

Y, X, m, n, o, p, q, r, s and R_1-R_{12}, have the meanings mentioned above.,

Alternatively the compounds of formula (C) may be obtained by reacting a compound of formula (F)



(F)

wherein W is OH or halogen, with a compound selected from alkyl and aryl sulfonylchloride, trifluoromethansulfonic acid anhydride, when W is OH or $AgSbF_6$, $AgBF_4$, $AgClO_4$, CF_3SO_3Ag, $AgSO_3CH_3$, $CH_3C_6H_4SO_3Ag$ when W is halogen.

Nitration of compound (D) was performed in an organic solvent, generally in a solvent selected from acetone, tetrahydrofurane, dimethylformamide, N-methylpyrrolidone, sulfolane, acetonitrile, methylene chloride etc., with nitrating agents selected from transition metal salts or, when M is OH, with nitrating systems based on nitric acid, such as the sulfonitric mixture.

The (D)/nitrating agent molar ratio is of from 2 to 0.5, in particular of 1.5 to 0.5 and the nitration is carried at a temperature ranging from 0°C to 100°C, preferably from 15°C to 80°C.

The reaction product (C) may be isolated or its solution can be employed as such for the reaction with substrate (B) to give (A).

Nitration of compound (E) may be carried out in an organic solvent, generally in a solvent selected from acetone, tetrahydrofurane, dimethylformamide, N-methylpyrrolidone, sulfolane, acetonitrile, methylene chloride etc., with nucleophilic nitrating agents such as alkaline metal nitrates, onium salt nitrates, for example tetraalkylammonium, tetraalkyl-phosphonium or trialkylammonium nitrate and so on.

The reaction is carried out at a temperature of from 0°C to 100°C, in particular of 15°C to 80°C and at a molar ratio (E)/nitrating agent of from 20 to 2, preferably of 8 to 1.

The reaction product (C) may be isolated or its solution can be employed such as in the reaction with substrate (B) to give (A).

The reaction for obtaining compound (C) from (F) may be carried out in an organic solvent, generally selected from the group consisting of acetone, tetrahydrofurane, dimethylformamide, N-methylpyrrolidone, sulfolane, acetonitrile, methylene chloride and the like, with a transition metals salts selected from those of silver, zinc, mercury or, when W is OH, the reaction was performed with an acid chloride such as methanesulfonyl chloride etc., or with a suitable anhydride such as trifluoro-methanesulfonic anhydride.

The reaction was performed at a temperature ranging from -20°C to 100°C, in particular from -20° to 60°C at a molar ratio compound (F)/reagent of from 2 to 0.5, preferably of 1.5 to 0.5.

The reaction product (C) may be isolated or its solution can be employed as such in the reaction with substrate (B) to give (A).

E X A M P L E S

Preparation of 4-nitrooxybutyl bromide according to Chem. Pharm. Bull.,1993,41,1040

Nitric acid (90%, 0.8 mol) was dropped under stirring in sulfuric acid maintained at 0°C (0.8 mol) and the mixture was then stirred at 0°C for 80 minutes. In the solution thus obtained and maintained at 0°C, under stirring 4-bromobutanol was dropped (0.4 mol) and the mixture was stirred again for additional 210 minutes at the same temperature. The solution was then poured in a water-ice mixture and extracted twice with diethyl ether. The ether extracts were combined together and washed with a sodium bicarbonate saturated solution. The solvent was evaporated off under vacuum to give a yellow oil (yield: 84.8%).

Example 1

Preparation of 4-nitrooxybutyl p-toluenesulfonate

To a solution of 4-bromobutanol (5.0 g, 33 mmol) in pyridine (50 ml) kept at 0°C, under stirring and under nitrogen atmosphere tosyl chloride (6.8 g, 36 mmol) was added. The resulting solution was kept under stirring for further 20 minutes and then stored overnight at -18°C. The reaction mixture was poured in a water/ice mixture (about 400 ml) and extracted with ethyl ether (500 ml). The organic phase was washed with 6N hydrochloric acid (500 ml) and dried on sodium sulfate. Evaporation of the solvent under vacuum, provided an oily residue (7 g). To a solution of the oily residue (7 g, 23 mmol) in acetonitrile (50 ml), kept under stirring and under nitrogen at room temperature, silver nitrate (7.8 g, 46 mmol) was added. After nearly 15 minutes, the formation of a yellow, insoluble product was observed. The heterogeneous mixture was kept under stirring overnight. The insoluble was removed by filtration and the solution was poured in water (200 ml) and extracted with ethyl ether (2x250ml). The combined organic extracts were dried over sodium sulfate. Evaporation of the solvent under vacuum afforded an oily residue (5 g).

Chromatography of the residue on silica gel (100 g), with hexane/ethyl ether mixture as eluent, gives the title product (3 g), m.p. 38-40°C and a purity, determined by HPLC, higher than 98%,.

FTIR (solid KBr, cm -1): 2966, 1626, 1355, 1281, 1177,1097, 959, 876, 815, 663, 553.

300 MHz 1H NMR (CDCl3) delta 1,77 (m, 4H); 2,35 (s, 3H); 4,06 (m, 2H); 4,38 (m, 2H); 7,36 (2H); 7,7 (2H).

Example 2

Synthesis 2-(S)-(6-methoxy-2-naphthyl)propanoic acid,4-(nitrooxy)butyl ester

$KHCO_3$ (5.22 g, 52 mmol) was added under nitrogen to a solution of 2-(S)-(6-methoxy-2-naphthyl)propanoic acid (Naproxen) (99 e.e. determined by chiral HPLC) (10.0 g, 43 mmol) in DMF (200 ml).

The heterogeneous mixture was heated up to 50-60°C and kept at this temperature under nitrogen and under magnetic stirring for 90 min.The reaction mixture was allowed to cool down to room temperature. Potassium iodide (2.14 g, 12.9 mmol) and 4-bromobutylnitrate (14.48 g 73 mmol) were added to the above mixture, and the reaction mixture was stirred at room temperature under nitrogen for 25 h. Water (200ml) was added dropwise in 5 min. to the reaction mixture. The mixture was extracted with t-BuOMe (200 ml), the organic phase was washed with NaCl 10% aqueous solution (2 x 200 ml) and was dried over Na_2SO_4. Evaporation of the solvent in vacuo provided an oily residue (17.3 g). Chromatography on silica gel (eluent hexanes/ethyl acetate) of the residue provided 2-(S)-(6-methoxy-2-naphthyl)propanoic acid,4-(nitrooxy)butyl ester as an yellow oily compound (10.8 g, 73 % yield, e.e., determined by HPLC,,higher than 99%).

The product was identified by comparison with an authentic sample.

Example 3

Synthesis 2-(S)-(6-methoxy-2-naphthyl)propanoic acid,4-(nitrooxy)butyl ester

$KHCO_3$ (5.22 g, 52 mmol) was added under nitrogen to a solution of 2-(S)-(6-methoxy-2-naphthyl)propanoic acid (Naproxen) (99 e.e. determined by chiral HPLC) (10.0 g, 43 mmol) in DMF (200 ml).

The heterogeneous mixture was heated up to 50-60°C and kept at this temperature under nitrogen and under magnetic stirring for 90 min.The reaction mixture was allowed to cool down to room temperature. 4-(nitooxy)butyl-4-methylbenzenesulphonate (21.1 g 73 mmol) was added to the above mixture, and the reaction mixture was stirred at room temperature under nitrogen for 25 h. Usual aqueos work up followed by chromatography on silica gel (eluent hexanes/ethyl acetate) of the reaction crude provided 2-(S)-(6-methoxy-2-naphthyl)propanoic acid,4-(nitrooxy)butyl ester (10.4 g, 70 % yield, e.e., determined by HPLC, higher than 99%).

Example 4

Synthesis 2-(S)- (+)-(5-bromo-6-methoxy-2-naphthyl)propanoic acid,4-(nitrooxy)butyl ester

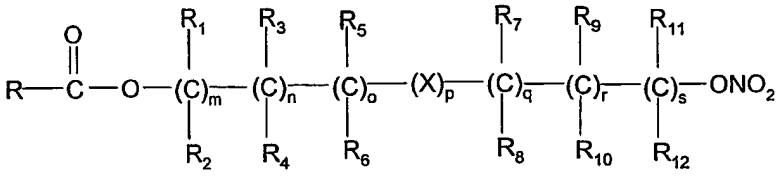
A mixture of triethylamine (5.25 g, 52 mmol), of 2-(S)-(5-bromo-6-methoxy-2-naphthyl)propanoic acid (Bromo-Naproxen) (13.3 g, 43 mmol); e.e.99%) and of 4-bromobutylnitrate (43 mmol) in DMF (120 ml) was stirred under nitrogen for 2 days at 25°C.

Removal of DMF under vacuum followed by usual aqueous work up provided the reaction crude.Chromatography on silica gel (eluent hexanes/ethyl acetate) of the residue provided pure 2-(S)-(5-bromo-6-methoxy-2-naphthyl)propanoic acid,(nitrooxy)butyl ester (11.9 g; 65% yield; e.e., determined by HPLC, higher than 99%).

The product was identified by spectroscopic methods.

CLAIMS

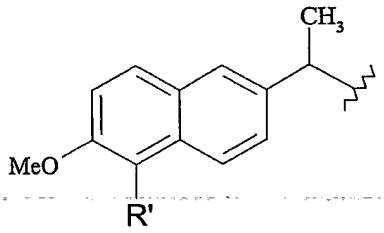
1. A process for preparing a compound of general formula (A)



(A)

wherein:

R is



in which R' is a hydrogen atom or Br

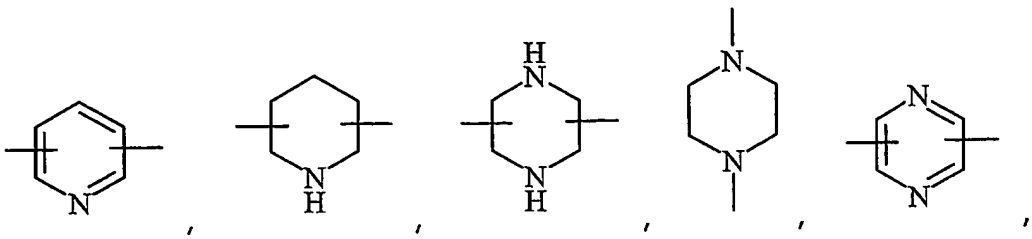
R_1-R_{12} are the same or different and independently are hydrogen, straight or branched C_1-C_6 alkyl, optionally substituted with aryl;

m, n, o, q, r and s are each independently an integer from 0 to 6, and p is 0 or 1, and

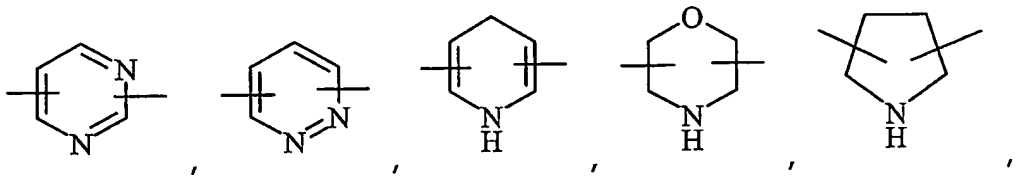
X is O, S, SO, SO_2, NR_{13} or PR_{13}, in which R_{13} is hydrogen, C_1-C_6 alkyl, or X is selected from the group consisting of:

- cycloalkylene with 5 to 7 carbon atoms into cycloalkylene ring, the ring being eventually substituted with side chains T, wherein T is straight or branched alkyl with from 1 to 10 carbon atoms;
- arylene, optionally substituted with one or more halogen atoms, straight or branched alkyl groups containing from 1 to 4 carbon atoms, or a straight or branched C_1-C_3 perfluoroalkyl;

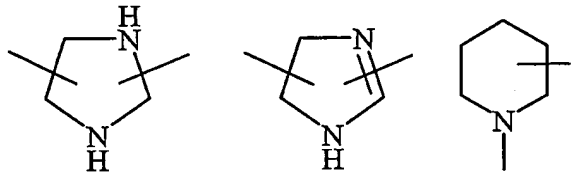
- a 5 or 6 member saturated, unsaturated, or aromatic heterocyclic ring selected from



(X1) (X2) (X3) (X4) (X5)



(X6) (X7) (X8) (X9) (X10)



(X11) (X12) (X13)

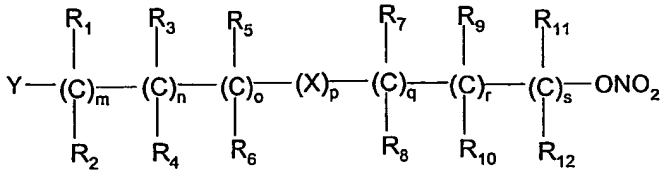
said process comprising:

i) reacting a compound of formula (B)

R-COOZ (B)

wherein R is as above defined and Z is hydrogen or a cation selected from Li+, Na+, Ca++, Mg++, tetralkylammonium, tetralkylphosphonium,

with a compound of formula (C)



(C)

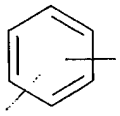
wherein R_1-R_{12} and m,n,o,p,q,r,s are as defined above and Y is selected from

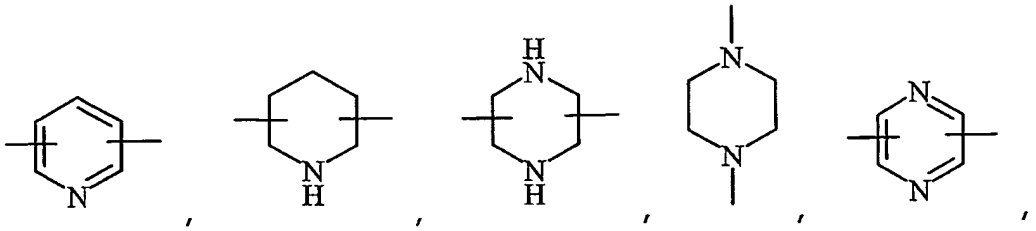
- a halogen atom

- $-BF_4$, $-SbF_6$, FSO_3-, R_ASO_3-, in which R_A is a straight or branched C_1-C_6 alkyl, optionally substituted with one or more halogen atoms, or a C1-C6 alkylaryl;
- R_BCOO^-, wherein R_B is straight or branched C_1-C_6 alkyl, aryl, optionally substituted with one or more halogen atoms or NO_2 groups, C_4-C_{10} heteroaryl and containing one or more heteroatoms, which are the same or different, selected from nitrogen, oxygen sulfur or phosphorus;
- aryloxy optionally substituted with one or more halogen atoms or NO_2 groups, or heteroaryloxy and

ii) optionally converting a compound of formula (A) wherein R' is Br in a compound of formula (A) wherein R' is hydrogen.

2. A process for preparing a compound of formula A according to claim 1 wherein:
the substituents R_1-R_{12} are the same or different and independently are hydrogen or straight or branched C_1-C_3 alkyl,
m, n, o, p, q, r and s are as defined above,
X is O, S or





(X1) (X2) (X3) (X4) (X5)

3. A process for preparing a compound of formula A according to claim 1 or 2 wherein R_1-R_4 and R_7-R_{10} are

hydrogens, m, n, q, r, are 1, o and s are 0, p is 0 or 1, and X is O or S.

4. A process for preparing a compound of formula A according to anyone of the preceding claims wherein Y is selected from the group consisting of Br, Cl, I, $-BF_4$, $-SbF_6$, FSO_3-, ClO_4-, CF_3SO_3-, $C_2F_5SO_3-$, $C_3F_7SO_3-$, $C_4F_9SO_3-$, $p-CH_3C_6H_4SO_3-$.

5. A process for preparing a compound of formula A according to anyone of the preceding claims wherein the reaction is performed in an organic solvent selected from acetone, tetrahydrofurane, dimethylformamide, N-methylpyrrolidone, sulfolane and acetonitrile.

6. A process for preparing a compound of formula A according to anyone of the claims 1-4 wherein the reaction is performed in a biphasic system comprising an aprotic dipolar solvent selected from toluene, chlorobenzene, nitrobenzene, tert-butylmethylether and a water solution wherein the organic solution contains (C) and the water solution contain an alkaline metal salt of (B), in presence of a phase transfer catalyst.

7. A process for preparing a compound of formula A according anyone of the preceding claims wherein the reaction is performed at a temperature ranging from 0°C to 100°C.

8. A process for preparing a compound of formula A according to anyone of the preceding claims wherein the compounds of formula B and C are reacted at a (B)/(C) molar ratio of 2-0.5.

9. 2-(S)-(5-bromo-6-methoxy-2-naphthyl)propanoic acid,4-(nitrooxy)butyl ester.

INTERNATIONAL SEARCH REPORT

In ial Application No
PCT/EP 03/08698

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 C07C201/02 C07C203/04

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 7 C07C

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)
EPO-Internal, WPI Data, BEILSTEIN Data, PAJ, CHEM ABS Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

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Y	KAWASHIMA ET AL: "Synthesis and Pharmacological Evaluation of (Nitrooxy)alkyl Apovincaminates" JOURNAL OF MEDICINAL CHEMISTRY, AMERICAN CHEMICAL SOCIETY. WASHINGTON, US, vol. 36, 1993, pages 815-819, XP002210204 ISSN: 0022-2623 page 815, scheme I, route A and B, page 817, right-hand column, lines 8-42	1-8

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[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

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Date of the actual completion of the international search	Date of mailing of the international search report
20 January 2004	04/02/2004

Name and mailing address of the ISA	Authorized officer
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INTERNATIONAL SEARCH REPORT

Inte onal Application No
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C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

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X	ABADI, ASHRAF H. ET AL: "Synthesis and cyclooxygenase inhibitory properties of novel (+) 2-(6-methoxy-2-naphthyl)propanoic acid (naproxen) derivatives" ARCHIV DER PHARMAZIE , vol. 334, no. 3, 2001, pages 104-106, XP002267383 page 105, scheme 1, reaction of 4 to 5	1-8
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Inte[illegible]nal Application No
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